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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,710	09/07/2004	Shyam B Karki	21087	4903

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EXAMINER	
BERNHARDT, EMILY B	
ART UNIT	**PAPER NUMBER**
1624	

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06/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,710	KARKI ET AL.	
	Examiner	Art Unit	
	Emily Bernhardt	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *20-24,30,31,35 and 39-45* is/are withdrawn from consideration.

5)☒ Claim(s) *7-10* is/are allowed.

6)☒ Claim(s) *1-6,11-19,25-29,32-34 and 36-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/31/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-19,25 (in part),26-29,32 (in part),33-34 and 36-38, drawn to 4-methanesulfonyl piperazine salt forms, simple and complex compositions and use for treating ocular diseases and various processes of making.

Group II, claim(s) 25 (in part),30,31, 32 (in part),35 and 39-45, drawn to additional uses employing compounds of I and optionally additionally active ingredients.

If Group II is elected applicants must pick a single use .

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Where more than one use exists only the first recited use is considered to form part of the main invention. See 37 CFR 1.475(d).

During a telephone conversation with Ms. Ayler on 5/15/07 a provisional election was made with right of traverse to prosecute the invention of I, claims 1-19,25 (in part), 26-29,32 (in part),33-34 and 36-38. Affirmation of this election must be made by applicant in replying to this Office action. Claims 20-24,30-31,35 and 39-45 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Ms. Ayler requested that ocular diseases be examined and the examiner agreed to such an examination. Claims 25 and 32 which link inventions I and II will only be examined with respect to the elected invention.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Applicants request for a corrected filing receipt in order to have the title corrected is noted. The examiner will alert the PTO staff to make the correction.

Claims 1-6, 25 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
1. Claims 25 and 32 are of unclear scope for more than one reason. Defining a disease(s) by its (their) underlying cause renders the scope of intended uses indeterminate since the claim language may read on diseases not yet known to be caused by or affected by such action or in ways not yet understood. Additionally, determining whether a given ocular disease (the elected use) responds or not to increased angiogenesis or inhibition of one or more tyrosine kinases (of which many types exist)

involves much experimentation since a negative response from one patient does not mean the drug isnt useful as no drug has 100% effectiveness. Thus what success rate determines if a particular inhibitor is effective and how many patients (and dosage regimens) need to be tested? The test for determining compliance with 35 USC 112, par.two is whether applicants have clearly defined "their" invention not what may be discovered by future research as this type of claim language clearly requires.

2. Claims 1 vs 2 as well as 3 vs 4 as well as 5 vs 6 apper to be substantial duplicates since for each set of claims the only difference is the added DSC data. It appears the DSC data is an inherent characteristic and thus would not fail to distinguish (i.e. further limit) the claim(s) reciting the X-ray data. Thus it is not seen how infringing one of the pair would not infringe the remaining claim.

3.For the form present in claims 3 and 4 specification identifies such as a hydrate form not recited in the claims.

Claims 25 and 33 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 32 and 34, respectively. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper

after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Appropriate correction is required.

Claims 25-29 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating but **not** preventing the ocular diseases recited in claims 27-29, does not reasonably provide enablement for treating much less **preventing** any and all ocular disorders also embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The notion that tyrosine kinase (TK) inhibitors as a class (VEGF in particular) can be employed for such uses is not substantiated by the art. See for example, Strawn, provided with this action. Note especially concluding remarks on p.565, left column, first paragraph. Also Note Dredge who stresses that antiangiogenic agents do not necessarily possess a broad spectrum of uses as discussed on p.961, section 6 of the article. Thus simply being able to inhibit the binding of one or more tyrosine kinases is not a reasonable basis to conclude that all claimed uses

can be treated (much less prevented) given the nature of applicants' testing which is all assay testing and the current state of the art does not warrant such an assertion. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of in vivo efficacy by those skilled in the art. See for example, In re Ruskin 148 USPQ 221; Ex parte Jovanovics 211 USPQ 907. Any evidence relied on by applicants must clearly show a reasonable expectation of in vivo success for any additional diseases that may still be embraced in response to this action. See MPEP. 2164.05(a). Note also the criteria for enablement as set out in In re Wands cited in MPEP 2164.01(a),August 2000 edition which considers factors such as:

1) Breadth of the claims- The claims cover (but are not limited to) to all types of ocular diseases, inflammatory and bone disorders,etc.;

2) Level of skill in this art- the examiner has pointed out above that drugs having the activity relied on herein are not known to have such a spectrum of clinical applications and thus the level of skill is low ;

3) Working examples- There are no test(s) directed to the many uses pointed out above which are art-recognized for predicting *in vivo* efficacy .

Thus in view of the above, the rejection is being applied.

Claims 1-6,11-19,25-29,32-34 and 36-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specification provides no reasonable assurance that the many forms being claimed, namely forms B, D and E will be sufficiently stable to be useful for their intended purposes- for treating diseases based on TK inhibition, for use in formulations either alone or with other additional active ingredients. It is well known that only one polymorph is the most thermodynamically stable at a given temperature and pressure and that other forms of lesser stability may change form upon milling/ grinding when preparing compositions as well as simply on standing. Note Rouhi provided with this action which discusses the many pitfalls in dealing with polymorphs for commercial use. The unpredictable nature of which metastable form may survive handling is especially discussed. In the present specification only Form A (not being claimed but only process for making it) has been tested for stability as mentioned on pp.34-35. Other forms have not and Form E in water is stated to transform into Form D. See

p.37.Pursuant to In re Wands (8 USPQ 2d 1400), thus given the nature of the invention (discovery of several polymorphic forms of an old compound); the level of unpredictability in the art as evidence by Rouhi and the lack of working examples showing reasonable stability at ordinary storage/process conditions this rejection is being applied.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1,2 and 17-19,33-34 and 36-38 are rejected under 35 U.S.C. 102(e) as being anticipated by Fraley (WO'861). The commonly assigned publication (cited by applicants) is applied as of its US provisional priority date of 10/17/00. It describes 2 forms of the HCl salt having the same structure as herein for uses based on TK inhibition as well use of said compounds for treating ocular diseases- either alone or with other drugs. See pages 5-9 and in particular pages 40-42 which describes data

for the 2 forms identified as 1-11C and 1-11D. A comparison of the X-ray pattern for 1-11D shows it to be similar to instant Form B covered in claims 1 and 2 and claims dependent thereon. However the melting endotherm for 1-11C (reported as 284°) is very close to instant Form B. The x-ray pattern is depicted as Figure 3 but not seen in tabular form. In the absence of any data reporting experimental fluctuations for either piece of data- the DSC or X-ray powder, it cannot be conclusively established that instant Form B isn't one of the two forms reported by Fraley. Composition claims 18,19,33,34 and 36-38 are also rejected herein despite their ultimate dependency from claim 3 since once in liquid solution, the polymorphic identity disappears such that the solutions are the same regardless which form was originally present. Carriers include liquid forms as described in the specification.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d

937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 2 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2,5 and 6 of U.S. Patent No. 6,656,942. Although the conflicting claims are not identical, they are not patentably distinct from each other because the HCl salts being claimed in US'942 correspond to those discussed in WO'861 applied above. It is noted that there are no method claims in the instant case directed to Form B. US'942 has no composition claims for the HCl salt.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6,17-19,25-29,32-34 and 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arrington (WO'025). The commonly assigned publication (cited by applicants-see ref. U in IDS of 2/18/05) published more than a year earlier than applicants' 371 filing date. It describes the free from of instant HCl salts for the same uses.See pages 15-18 and in particular example 5-10 on p.83 which is directed to the free base and the preparation of the TFA salt. While HCl salts are not made, Arrington includes such as part of the invention as can be seen on p.23 directed to salts. Thus it would have been obvious to one skilled in the art at the time the instant invention was made to also make other salts of exemplified compounds including the HCl salt. Following the teachings of Arrington to prepare the TFA salt using reverse-phase chromatography as detailed in the example one would expect to also make the HCl salt in a similar manner. It may well be that resulting salt may be one of the forms claimed herein. To overcome this rejection applicants need to show that following the teachings of Arrington and obvious modifications thereof, instant HCl salts are **not** obtained.

Claims 7-10, directed to making Form A, are allowed as no suggestion of using DMSO in the closest art applied is seen.

Applicants' IDS filed 2/18/05 has not been completely considered as the follwing references are not seen: ref.13,28 and 72.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Bernhardt whose telephone number is 571-272-0664.

If attempts to reach the examiner by telephone are unsuccessful, the acting supervisor for AU 1624, James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

E Bernhardt

Emily Bernhardt
Primary Examiner
Art Unit 1624